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[54] GUANYLHYDRAZONES AND THEIR USE TO TREAT INFLAMMATORY CONDITIONS

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[56] References Cited

U.S. PATENT DOCUMENTS

3,799,988 3/1974 Hashimoto et al. 564/151

OTHER PUBLICATIONS

Berger et al., 1991, "Hydroxylation of Pentamidine by Rat Liver Microsomes" *The Journal of Pharmacology and Experimental Therapeutics* 256: 883–889.

Beutler and Cerami, 1988, "The Common Mediator of Shock, Cachexia and Tumor Necrosis", *Advances in Immunology* 42: 213–231.

Billiar et al., 1990, "Modulation of Nitrogen Oxide Synthesis In Vivo: N^G -Monomethyl-L-Arginine Inhibits Endotoxin-Induced Nitrite/Nitrate Biosynthesis While Promoting Hepatic Damage", *Journal of Leukocyte Biology* 48: 565–569.

Bouskela and Rubanyi, 1994, "Effects of N_{γ} -Nitro-L-Arginine and Dexamethasone on Early Events Following Lipopolysaccharide Injection: Observations in the Hamster Cheek Pouch Microcirculation" SHOCK 1: 347–353.

Brennan, M. F., 1981, "Total Parenteral Nutrition in the Cancer Patient", *The New England Journal of Medicine* 305: 375–382.

Cobb et al., 1992, "N^o-Amino-L-Arginine, an Inhibitor of Nitric Oxide Synthase, Raises Vascular Resistance but Incereases Mortality Rates in Awake Canines Challenge with Endotoxin", *J. Exp. Med.* 176: 1175-1182.

Darling et al., 1990, "Cachectic Effects of Recombinant Human Tumor Necrosis Factor in Rats", *Cancer Research* 50: 4008–4013.

Detsky et al., 1987, "Perioperative Parenteral Nutrition: A Meta-Analysis", Annals of Internal Medicine 107: 195–203. Ding et al., 1988, "Release of Reactive Nitrogen Intermediates and Reactive Oxygen Intermediates from Mouse Peritoneal Macrophages", The Journal of Immunology 141: 2407–2412.

Granger et al., 1990, "Metabolic Fate of L-Arginine in Relation to Microbiostatic Capabilite of Murine Macrophages", *J. Clin. Invest.* 85: 264–273.

Hibbs et al., 1987, "Macrophage Cytotoxicity: Role for L-Arginine Deiminase and Imino Nitrogen Oxidation to Nitrite". *Science* 235: 473–476.

Kemp and Petrakis, 1981, "Synthesis and Conformational Analysis of *cis,cis*-1,3,5-Trimethylcyclohexane-1,3,5-tri-carboxylic Acid", *J. Org. Chem.* 46: 5140-5143.

Kilbourn et al., 1990, "Reversal of Endotoxin–Mediated Shock by N^G–Methyl–L–Arginine, An Inhibitor of Nitric Oxide Sythesis", *Biochemical and Biophysical Research Communications* 172: 1132–1138.

Koretz, R. L., 1984, "Parenteral Nutrition, Is it Oncologically Logical?" *Jornal of Clinical Oncology* 2: 534–538. Korytnyk et al., 1978, "guanylhydrazones with Potential Antileukemic Activity. 2. Synthesis and Structure–Activity Relationships of Analogues of 4,4'–Diacetyl–N, N'–diphenylurea Bis(guanylhydrazone)^{1,2}", Journal of Medicinal Chemistry 21: 507–513.

Kubes et al., 1992, "Participation in α_2 -adrenergic receptors in neural vascular tone of canine skeletal muscle", *The Americal Journal of Physiology* 262: H611-H615

Langstein et al., 1989, "Reversal of Cancer Cachexia by Antibodies to Interferon–Gamma but not Cachectin/Tumor Necrosis Factor", *Surgical Forum* 15: 408–410.

McGeer et al., 1989, "Parenteral Nutrition in Patients Receiving Cancer Chemotherapy", *Annals of Internal Medicine* 110: 734–736.

Minnard et al., 1994, "Inhibition of Nitric Oxide Synthesis Is Detrimental During Endotoxemia", *Arch. Surg.* 129: 142–148.

Nathan, Carl, 1992, "Nitric oxide as a secretory product of mammalian cells", *The FASEB Journal* 6: 3051–3064.

Sherry et al., 1989, "Anticachectin/tumor necrosis factor— α antibodies attenuate development of cachexia in tumor models", *The FASEB Journal* 3: 1956–1962.

Ulrich and Cerami, 1984, "Trypanocidal 1,3-Arylene Diketone Bis(Guanylhydrazone)s. Structure-Activity Relationships among Substituted and Heterocyclic Analogues" *Journal of Medicinal Chemistry* 27: 35–40.

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[57] ABSTRACT

This invention concerns new methods and compositions that are useful in preventing and ameliorating cachexia, the clinical syndrome of poor nutritional status and bodily wasting associated with cancer and other chronic diseases. More particularly, the invention relates to aromatic guanylhydrazone (more properly termed amidinohydrazone) compositions and their use to inhibit the uptake of arginine by macrophages and/or its conversion to urea. These compositions and methods are also useful in preventing the generation of nitric oxide (NO) by cells, and so to prevent NO-mediated inflammation and other responses in persons in need of same. In another embodiment, the compounds can be used to inhibit arginine uptake in arginine-dependent tumors and infections.

6 Claims, 22 Drawing Sheets